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# Alcohol, Other Drugs, and Health: Current Evidence

JULY-AUGUST 2018

## INTERVENTIONS & ASSESSMENTS

### A 7-day Opioid Withdrawal Management Protocol With Escalating Doses of Naltrexone Did Not Help With Transition to Long-acting Naltrexone

Long-acting injectable naltrexone (XR-NTX) has been shown to be an effective treatment for opioid use disorder, but transition to this treatment is complicated by the need to abstain from opioids prior to initiation. Researchers recruited adults with *DSM-IV* opioid dependence seeking treatment with XR-NTX and compared with placebo a protocol using gradually escalating doses of oral naltrexone (NTX), with and without a 3-day buprenorphine taper (BUP). Of 653 participants assessed, 378 were randomized to NTX/BUP, NTX/placebo BUP, or placebo NTX/placebo BUP. All received ancillary medications, including clonidine, trazodone, and clonazepam. The primary endpoint was initiation of XR-NTX.

- Transition to XR-NTX was achieved by 44% of participants and 18% received 3 monthly injections; there was no significant difference in either outcome between the 3 groups.
- Participants in the NTX/BUP group were significantly more likely to be abstinent during the 7-day transition period.

*Comments:* The difficulty with transitioning to treatment remains a major limitation of XR-NTX. For most individuals, agonist treatment with buprenorphine or methadone will remain the treatment of choice until better transition protocols can be found.

Darius A. Rastegar, MD

*Reference:* Bisaga A, Mannelli P, Yu M, et al. Outpatient transition to extended-release naltrexone for patients with opioid use disorder: a phase 3 randomized trial. *Drug Alcohol Depend.* 2018;187:171–178.

### Middle School Interventions Reduce Rates of Alcohol Use Disorder at High School Graduation

Early initiation of alcohol use is associated with an increased risk of alcohol use disorder (AUD) later in life. Prevention programs delivered in middle school may be able to disrupt this relationship, although most studies examine immediate outcomes and intermediary markers. In this study, Mexican-American adolescents who participated in a randomized controlled trial of an alcohol prevention program in middle school were re-surveyed as high school seniors.

- Compared with controls, students who were randomized to the preventive intervention were 2.5 times less likely to have had an AUD by senior year of high school.
- Among students who had initiated alcohol use in middle school, students randomized to the intervention group reported less frequent alcohol use and “drunkenness”\* in twelfth grade compared with those randomized to the control group.
- There were no differences in frequency of alcohol use or “drunkenness” among students who initiated alcohol use after middle school.

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## Middle School Interventions Reduce Rates of Alcohol Use Disorder at High School Graduation (continued from page 1)

\* Based on responses to the 2001 Youth Risk Behavior Survey question: "During the past year, on how many days did you drink enough to feel pretty high/drunk?"

*Comments:* Adolescence is a developmental window during which children are particularly vulnerable to the development of substance use disorder. Interventions that reduce use during this critical period may reduce lifetime risk for substance use disorder, and thus may have benefits that compound over time.

Sharon Levy, MD, MPH

*Reference:* Gonzales NA, Jensen M, Tein JY, et al. Effect of middle school interventions on alcohol misuse and abuse in Mexican American high school adolescents: five-year follow-up of a randomized clinical trial. *JAMA Psychiatry*. 2018;75(5):429–443.

## HEALTH OUTCOMES

### Medical Marijuana Use Associated With Medical and Non-medical Use of Prescription Drugs

Several recent ecological and cross-sectional studies have suggested that states with medical marijuana laws have both decreased prescription drug use (medical and non-medical) and decreased harms, including overdose, compared with states without medical marijuana laws. Although these studies have generated press, methodological concerns exist regarding the validity of inferences drawn from population-level policy data applied to individual behavior. Researchers examined individual-level data from the 2015 National Survey on Drug Use and Health to determine the association between medical marijuana use and risk of medical and nonmedical prescription drug use. Risk ratios [RR] were calculated adjusting for age, sex, race, health status, family income, and living in a state with legalized medical marijuana. Compared with those without medical marijuana use:

- Individuals with medical marijuana use had an elevated risk of self-reported prescription medication use in the past 12 months (RR, 1.62).
- Individuals with medical marijuana use were more likely to report nonmedical use of any prescription medications in the past 12 months (RR, 2.12), specifically, with elevated risks for pain relievers (RR, 1.95), stimulants (RR, 1.86), and tranquilizers (RR, 2.18).

*Comments:* These findings challenge the notion that medical marijuana protects against opioid-related harms. Although this study was retrospective and relied on self-report data, it should prompt clinicians to screen for polypharmacy and non-medical prescription drug use among patients with medical marijuana use.

Jeanette M. Tetrault, MD

*Reference:* Caputi TL and Humphreys K. Medical marijuana users are more likely to use prescription drugs medically and nonmedically. *J Addict Med*. 2018;12(4):295–299.

### Synergistic Association Between Hot Tea Drinking, Smoking, and Alcohol Use on Esophageal Cancer Risk

Alcohol and tobacco use are known risk factors for developing esophageal squamous cell cancer. Tea may have inhibitory effects in cancer development, but chronic thermal injury may also initiate carcinogenesis. This prospective study in China investigated associations between tea consumption and esophageal cancer, and potential interactions with smoking and alcohol use. The study comprised 456,155 people aged 30–79, followed for a median of 9.2 years. Overall, 1731 incident cases of esophageal cancer were identified (1106 in men, 625 in women).

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## Synergistic Association Between Hot Tea Drinking, Smoking, and Alcohol Use on Esophageal Cancer Risk

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- In those who didn't smoke and were drinking <15 g of ethanol in a day, there was no association between daily tea drinking and esophageal cancer, regardless of tea temperature.
- Participants drinking daily high-temperature tea in the presence of either smoking or drinking ≥15 g of ethanol in a day had an increased risk of esophageal cancer (hazard ratio [HR], 1.6 and 2.3, respectively).
- The strongest association was seen among those participants with a combination of daily high-temperature tea drinking, smoking, and alcohol use (HR, 5.0).

*Comments:* In this large prospective cohort, researchers found joint associations between high-temperature tea drinking, smoking, and alcohol use on esophageal cancer risk. No benefit of tea drinking was identified. The synergistic effects of hot tea drinking, smoking, and alcohol use on esophageal cancer risk are biologically plausible. In addition to prevention efforts targeting smoking and alcohol use, this calls for limiting hot tea drinking in people with regular alcohol use and/or smoking.

Nicolas Bertholet, MD, MSc

*Reference:* Yu C, Tang H, Guo Y, et al. Hot tea consumption and its interactions with alcohol and tobacco use on the risk for esophageal cancer: a population-based cohort study. *Ann Intern Med.* 2018;168(7):489–497.

## One Drink a Day Is Not Only Not Good for You, It's Bad for You

A drink a day has been thought to benefit cardiovascular risk and even overall survival, but recent systematic reviews focused on the most rigorous studies have raised serious doubts. Researchers performed individual-participant data analysis (n=599,912 people who currently drink, 71,011 with serial measurements) of 83 prospective cohort studies (5.4 million person-years of follow-up). Analyses were adjusted for age, sex, diabetes, and smoking.

- All-cause mortality increased linearly at >7 drinks/week.
- The risk for non-fatal myocardial infarction was 7% lower for each additional 7 drinks/week.
- >1 drink/week was associated with a linear increase in the risk for stroke.
- >1 drink/day was linearly associated with heart failure and death from other cardiovascular disease.
- The risk for other cardiovascular disease was 6% higher above 7 drinks/week. Approximately 6 drinks/week was associated with lower risk, but 5 was not associated with any protection or risk compared with lower amounts.
- Further adjustment, for cholesterol, fibrinogen, smoking amount, education, occupation, physical activity,

general health, red meat consumption, and anti-hypertensive use did not change the results.

- Reducing drinking from 14 to <7 drinks/week would increase life expectancy by 1-2 years for a 40-year-old man.

*Comments:* This study highlights a challenge in using observational data to study disease prevention with a pharmacological substance—the margins between doses (averages of self-reports) having different effects are slim. Randomized trials of ethanol for cardiovascular prevention are unlikely to be conclusive since a number of precise dose levels would need to be administered for years. These results suggest that aside from the known cancer risks of low amounts of drinking, just above a drink a day increases risk for cardiovascular disease and death. Public health recommendations for risky drinking limits (currently 14 drinks/week for men in the US) should likely be adjusted accordingly.

Richard Saitz, MD, MPH

*Reference:* Wood AM, Kaptoge S, Butterworth AS et al. Risk thresholds for alcohol consumption: combined analysis of individual-participant data for 599 912 current drinkers in 83 prospective studies. *Lancet.* 2018;391:1513–1523.

## The Comparative Effects of Buprenorphine and Methadone on Mortality

Opioid agonist treatment (OAT) with buprenorphine or methadone has been shown to have many benefits, including reducing mortality. However, relatively little is known about the comparative effects of these two agents. Researchers in the UK used data from primary care practices and national statistics to investigate the association between treatment with buprenorphine and methadone, and mortality. Treatment episodes were divided into 4 periods:

1) weeks 1–4 of OAT, 2) rest of time receiving OAT, 3) weeks 1–4 off OAT, 4) rest of time off OAT (up to 12 months).

- From 1998–2014, there were 11,033 people prescribed buprenorphine or methadone. The mean (and median) treatment duration was 363 (111) days for methadone and 173 (40) for buprenorphine; the mean

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## The Comparative Effects of Buprenorphine and Methadone on Mortality (continued from page 3)

daily dose was 65 mg for methadone and 8 mg for buprenorphine.

- There were 1.93 deaths/100 person-years while receiving OAT or within 12 months of cessation. Mortality was lowest from 4 weeks receiving OAT until cessation (0.98 deaths/100 person-years). Compared with receiving OAT, the adjusted mortality risk was 3.3 during weeks 1-4 of OAT, 10.4 weeks 1-4 off OAT, and 2.8 the rest of the time off OAT.
- Patients receiving buprenorphine had a lower mortality (unadjusted and adjusted) than those receiving methadone during each time period, particularly during weeks 1-4.

*Comments:* While some of these findings may be specific to practices in the UK, the most important messages are that OAT reduces mortality and that the initial period off of treatment is particularly dangerous. Buprenorphine may have some advantages, especially during treatment initiation, but this may be offset by shorter duration of treatment. These findings highlight the importance of maintaining treatment engagement.

Darius A. Rastegar, MD

*Reference:* Hickman M, Steer C, Tilling K, et al. The impact of buprenorphine and methadone on mortality: a primary care cohort study in the United Kingdom. *Addiction*. 2018;113(8):1461–1476.

## HIV AND HCV

### HIV Incidence Among People With HCV Who Use Drugs: an Opportunity for PrEP

Some people who inject drugs (PWID) remain at high risk of HIV acquisition. This is despite available evidence-based harm reduction strategies, including syringe exchange, medication for opioid use disorder, and low-barrier treatment programs in some locations in the US. Researchers described the HIV incidence among people who use heroin and/or cocaine engaged in a mobile harm reduction clinic (n=260). All participants were HIV-negative at baseline and had at least one subsequent HIV test.

- Half of participants (55%) injected drugs and 33% were HCV infected at baseline.
- Over 331 person-years of risk, 10 participants (4%) became HIV-positive, conferring an HIV incidence of 3 per 100 person-years.
- Participants who acquired HIV were more likely to have HCV infection (80% versus 31%) and to report injection drug use (90% versus 52%) at baseline.
- In multivariable analyses adjusting for age, sex, nationality, receipt of methadone treatment, and injection use,

baseline HCV status remained an independent predictor of time to HIV seroconversion (hazard ratio, 6.4).

*Comments:* HIV seroconversion in this cohort of people who used heroin and/or cocaine occurred in spite of access to harm reduction services. Baseline HCV infection emerged as an independent predictor of HIV seroconversion. HIV pre-exposure prophylaxis (PrEP) is an evidence-based strategy that reduces HIV acquisition among people with sexual and/or injection risk, but it has not been widely adopted for people who inject drugs. Study results suggest that HCV status may be one objective criteria that could be used to identify people who inject drugs who would benefit from intensified HIV prevention efforts like PrEP.

Jessica L. Taylor, MD

*Reference:* Valencia J, Ryan P, Alvaro-Meca A, et al. High HIV seroconversion rate in hepatitis C virus-infected drug users followed in a harm reduction unit: a lot opportunity for pre-exposure prophylaxis. *AIDS*. 2018; 32:9: 1157-1163.

### Isoniazid Preventive Therapy Among People With HIV and Heavy Alcohol Use in High Incidence Regions

Tuberculosis (TB) is the leading cause of death among people living with HIV (PLWH) worldwide and the risk is increased after starting antiretroviral therapy (ART). Isoniazid preventive therapy (IPT) is effective at reducing TB-related mortality but has long been contraindicated in patients with heavy alcohol use due to concerns for increased risk for hepatotoxicity. The World Health Organization recommends 36 months of empiric IPT—without diagnostic test-

ing for latent TB infection—for all PLWH in resource-limited countries without symptoms of active TB. However, 36 months of empiric therapy is rarely completed. Using a Markov simulation model, researchers examined the risks and benefits of providing IPT for either 6 months or 36 months at the initiation of ART, compared with ART alone, among PLWH with heavy alcohol use. The model was validated in 3 high TB-/HIV-burden countries: Brazil, India, and Uganda.

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## Isoniazid Preventive Therapy Among People With HIV and Heavy Alcohol Use in High Incidence Regions

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- In India and Uganda, 6 months of IPT combined with ART extended life expectancy over both ART alone and 36 months of IPT combined with ART. In Brazil, ART alone was superior.
- Toxicity occurred in 160/1000 persons receiving 6 months of IPT and 415/1000 persons receiving 36 months of IPT, with fatal toxicity in 8/1000 receiving 6 months and 21/1000 receiving 36 months of IPT.

*Comments:* The risk-benefit ratio of IPT for PLWH with heavy alcohol use favored 6 months of therapy (over 36

months) in India and Uganda but not in Brazil where TB incidence is lower. Further studies should assess population-level risks and benefits in high-burden countries to inform refined guideline development.

Jeanette M. Tetrault, MD

*Reference:* Freiman JM, Jacobson KR, Muyindike WR, et al. Isoniazid preventive therapy for people with HIV who are heavy alcohol drinkers in high TB-/HIV-burden countries: a risk-benefit analysis. *J Acquir Immune Defic Syndr*. 2018;77(4):405–412.

## PRESCRIPTION DRUGS & PAIN

### Medical Cannabis Laws May Be Associated With Reduced Opioid Dispensing in Patients Using Medicare Part D

Twenty-nine states and the District of Columbia have passed medical cannabis laws (MCL) permitting cannabis as a medical treatment for indications associated with chronic pain. Past studies have found an association between MCLs and reduced opioid prescribing and opioid-related harms. This analysis sought to identify changes in state-level opioid dispensing following MCL implementation among patients using Medicare Part D benefits in calendar years 2010–2015. The study examined two specific types of MCLs: those permitting patients to cultivate their own cannabis at home, and those in which a dispensary has actually been opened.

- Implementation of home cultivation was associated with a 7% reduction in daily opioid doses.

- Dispensary opening was associated with a 14% reduction in daily opioid doses.

*Comments:* These data further our understanding of the association between MCL and opioid prescribing by considering two specifics of MCL implementation: permitting home cultivation and opening of dispensaries. Causal inference from the observed association is limited by lack of data on uptake of medical cannabis and absence of controlling for myriad other efforts to address opioid prescribing over the same timeframe.

Marc R. Larochelle, MD, MPH

*Reference:* Bradford AC, Bradford WD, Abraham A, Bagwell Adams G. Association between US state medical cannabis laws and opioid prescribing in the Medicare Part D population. *JAMA Intern Med*. 2018; 178(5):667–673.

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